represent sufficient departures to warrant field testing. Enhanced correlation of existing animal models with immunogenicity in man would obviate such repetitive, time-consuming, logistically difficult, and expensive field studies.

2. Efforts should be made to reduce nonspecific reactogenicity of the toxoid. Standards should be established for purity of the toxoid in terms of Lf content per milligram of nitrogen.

3. Public support for the development of a more immunogenic toxoid should be considered. Of much lower priority is development of an immunizing agent against components of the organism other than the toxoid.

Monitoring of the diphteria immune status of the population by Schick testing or serologic testing would seem to be of maximum importance to prevent the development of a large population at risk in the future. The value of the Schick test is well established. However, the preparation of Schick test material is an understandably unprofitable undertaking for manufacturers. Public support may be necessary for continued production of this material, which is infrequently used but occasionally invaluable.

4. It is recommended that the apparent immunogenic superiority of the adsorbed toxoid over the fluid preparation be strongly emphasized and be included in labeling of products.

5. Finally, for the diphtheria toxoids whose effectiveness can be established by simple blood tests, there must be a resolution of the conflict in public policy between insistence on effectiveness data and contraints on obtaining such data resulting from the complex issue of informed consent. (See section 2.b. (2) in the Introduction to this Report.)

Basis for Classification

Past experience indicates that all diphtheria toxoids that meet the Bureau of Biologics' requirements for potency in animal tests have proved effective as boosters in man. Therefore, all currently licensed and marketed products are classified in Category I as regards their use for secondary or booster immunization.

However, quantitative correlation between primary immunogenicity in man and the results of animal protection tests has not been established; therefore direct testing of antitoxin responses in man is required, and should be repeated whenever significant changes in the manufacturing process are made. For these products, therefore, for which such evidence of effectiveness in primary immunization has not been acquired, Category IIIA is recommended.

References

(1) Barksdale, L., "*Corynebacterium diphtheriate* and its Relatives," *Bacteriological Reviews*, 34:378–422, 1970.

(2) Smith, J.W.G., "Diphtheria and Tetanus Toxoids," *British Medical Bulletin*, 25: 177–182, 1969.

(3) Public Health Service Advisory Committee on Immunization Practices, "Diphtheria and Tetanus Toxoids and Pertussis Vaccine," *Morbidity and Mortality Weekly Report*, Suppl. 21(25):4–5, June 24, 1972.

(4) Brooks, G.F., J.V. Bennett, and R.A. Feldman, "Diphtheria in the United States, 1959–1970," *Journal of Infectious Diseases*, 129:172–178, 1974.

(5) Center for Disease Control, "Reported Morbidity and Mortality in the United States, 1976," *Morbidity and Mortality Weekly Report*, Suppl., Health, Education, and Welfare Publication Number (Center for Disease Control) 77–8244, August 1977.

(6) "Diphtheria—Tetanus—Pertussis," *in* "Center for Disease Control, United States Immunization Survey: 1975," Health, Education, and Welfare Publication Number (Center for Disease Control) 76–8221, pp. 25–30, 1977.

(7) Miller, L.W., J.J. Older, J. Drake, and S. Zimmerman., "Diphtheria Immunization. Effect upon Carriers and the Control of Outbreaks," *American Journal of Diseases of Children*, 123:197–199, 1972.

(8) Edsall, G., J.S. Altman, and A.J. Gaspar, "Combined Tetanus—Diphtheria Immunization of Adults: Use of Small Doses of Diphtheria Toxoid," *American Journal of Public Health*, 44:1537–1545, 1954.

SPECIFIC PRODUCT REVIEWS

Diphtheria Toxoid Absorbed Manufactured by Bureau of Laboratories, Michigan Department of Public Health

Recommendations. The Panel recommends that this product be placed in Category IIIC and that the appropriate license be revoked for administrative reasons because this product is not marketed in the form for which licensed and consequently there are insufficient data on labeling, safety, and effectiveness.

Diphtheria Toxoid Manufactured by Connaught Laboratories Limited

1. *Description.* This product contains 40 to 50 Lf fluid diphtheria toxoid per mL. According to a revision of manufacturing procedures in 1973, the current product should contain 50 Lf per mL.

2. *Labeling*—a. *Recommended use/indications.* This preparation is recommended for active immunizations against diphtheria. Three doses of 1 cc (50 Lf) each at intervals of 4 weeks, beginning at 3 to 6 months of age. Reinforcing doses of 1 cc are given 1 year after the primary series and 4 years later. At school age an additional reinforcing dose of 0.1 to 0.2 mL may be given without being preceded by a reaction test.

b. *Contraindications.* Contraindications are not well outlined. Reaction tests are recommended in older children (over 8 years) and adults.

3. *Analysis*—a. *Efficacy*—(1) *Animal.* This product meets Federal requirements.

(2) *Human.* In studies (Ref. 1) carried out in 1964 to 1965, 68 children, ages 7 to 15 years, were evaluated for their diphtheria antitoxin levels after 3 injections of Connaught Laboratories DT—polio vaccine. Sera from 54 children had no preimmunization antibody, and were considered to be primary responders. Eighty-three percent had protective levels of diphtheria antibody 1 month after the third injection.

b. *Safety*—(1) *Animal.* This product meets Federal requirements.

(2) *Human.* No data relating specifically to this product are presented. The manufacturer states that adverse reactions have not been reported.

c. *Benefit/risk ratio.* The benefit-to-risk assessment of the product is satisfactory.

d. *Labeling.* There is some inconsistency in labeling in the submission as to exact Lf content. Contraindications should be listed.

4. *Critique.* This product meets United States standards for animal safety and potency and appears safe in humans. Serologic data show adequate antibody response. The package insert should mention contraindications, and it should be stated that the preferred product for immunizations of infants is a combination product (DTP).

5. *Recommendations.* The Panel recommends that this product be placed in Category I and that the appropriate license(s) be continued because there is substantial evidence of safety and effectiveness for this product. Labeling should be revised in accordance with currently accepted guidelines and the recommendations of this Report.

Diphtheria Toxoid Fluid Manufactured by Dow Chemical Company

1. *Description.* This manufacturer maintains a license for fluid diphtheria toxoid, although it has apparently never marketed the product as a monovalent antigen, either in the fluid or adsorbed form. Instead, it is supplied in 2 adsorbed products, 1 in combination with tetanus toxoid and the other with tetanus toxoid and pertussis vaccine. Techniques for preparation of the toxoid

for ultimate combination meet or exceed Federal requirements.

2. *Labeling*—a. *Recommended use/indications.* Nonexistent because the product is not marketed.

b. *Contraindications.* Nonexistent because the product is not marketed.

3. *Analysis*—a. *Efficacy*—(1) *Animal.* This product meets Federal requirements when tested after combination with tetanus toxoid and adsorption.

(2). *Human.* No data relating directly to this product are available.

b. *Safety*—(1) *Animal.* This product meets Federal requirements when tested after combination with tetanus toxoid and adsorption.

(2) *Human.* No data relating specifically to this product are available. There have been only 5 reports in a 10-year period of reactions to the adsorbed product combined with tetanus toxoid, and all 5 of these were insignificant.

c. *Benefit/risk ratio.* The benefit-to-risk assessment cannot be determined for this unmarketed product.

4. *Critique.* The manufacturer maintains a license for diphtheria toxoid, fluids although it has never been marketed in the monovalent form. Inasmuch as the manufacturer does maintain a license for 2 combined forms of adsorbed diphtheria toxoid, the Panel believes that maintenance of this license is superfluous.

5. *Recommendations.* The Panel recommends that this product be placed in Category IIIC and that the appropriate license be revoked for administrative reasons because this product is not marketed in the form for which licensed and consequently there are insufficient data on labeling, safety, and effectiveness.

Diphtheria Toxoid Manufactured by Istituto Sieroterapico Vaccinogeno Toscano "Sclavo"

No data have been provided by the manufacturer for diphtheria toxoid, for which they are presently licensed. In the absence of any information from the manufacturer, the Panel can make no determination regarding the relative benefits and risks of this product.

Recommendations. The Panel recommends that this product be placed in Category IIIC and that the appropriate license be revoked pending submission of evidence regarding the safety and effectiveness of this product.

Diphtheria Toxoid Adsorbed Manufactured by Istituto Sieroterapico Vaccinogeno Toscano "Sclavo"

1. *Description.* A diphtheria toxoid purified by the metaphosphoric acid method, containing 15 Lf of toxoid per 0.5 mL dose, and 2 mg aluminum hydroxide per 0.5 mL dose[1] (80 percent of maximum permitted amount). It is preserved in thimerosal at a concentration of 1:10,000.

2. *Labeling*—a. *Recommended use/indications.* For active immunization against diphtheria in children under 6, two 0.5 mL doses 6 to 8 weeks apart and a "booster" dose 1 year later. There is no discussion concerning choice of this product as aganist diphtheria toxoid or diphtheria and tetanus toxoid and pertussis vaccine. The container label should say "SHAKE WELL."

b. *Contraindications.* Acute or active infections and temporary immunosuppression; in situations involving prolonged immunosuppression an extra dose is recommended.

3. *Analysis*—a. *Efficacy*—(1) *Animal.* This product meets Federal requirements.

(2) *Human.* A "controlled study" (Ref. 2) is cited using this toxoid in combination with typhoid-paratyphoid A and B (TAB) for children all preiously immunized against diphtheria. Three to 4-fold increases in antitoxin titer were observed. Additional data submitted on DT and Td provided evidence of effectiveness.

b. *Safety*—(1) *Animal.* This product meets Federal requirements.

(2) *Human.* The lack of complaints or claims against the product suggest that it is presumably not unduly reactive.

4. *Benefit/risk.* The benefit-to-risk assessment of this product is satisfactory.

5. *Critique.* Additional data were provided to the Panel subsequent to the original submission. The data were submitted as part of a license application to FDA for DT and Td products, but in accordance with the guidelines established by the Panel regarding the extrapolation of data from the use of combined vaccines, there was sufficient information to show that this product is safe and effective.

6. *Recommendations.* The Panel recommends that this product be placed in Category I and that the appropriate license(s) be continued because there is substantial evidence of safety and effectiveness for this product. Labeling should be revised in accordance with currently accepted guidelines and the recommendations of the Report.

[1] The label submitted to the Panel is wrong. This product contains of $Al(OH)_3$ per dose. It is the Panel's understanding that the labeling has been corrected.

Diphtheria Toxoid Manufactured by Massachusetts Public Health Biologic Laboratories

1. *Description.* This is a fluid diphtheria toxoid, which is no longer issued. It contains 20 Lf of diphtheria toxoid per mL. No information on production details is provided. The diluting medium is sodium chloride, buffered with 0.05 M phosphate buffer The preservative is thimerosal in concentration 1:10,000.

2. *Labeling*—a. *Recommended use/indications.* No labeling is included in the submission.

b. *Contraindications.* No labeling.

3. *Analysis*—a. *Efficacy*—(1) *Animal.* This product meets Federal requirements.

(2) *Human.* Several published reports on the efficacy of the manufacturer's products are cited in the submission (Ref. 3). In the 1950's, this toxoid appeared efficacious in eliciting antitoxin response in persons who did not demonstrate measurable antitoxin in their blood.

b. *Safety*—(1) *Animal.* This product meets Federal requirements.

(2) *Human.* Safety data are presented (Ref. 3) from a multitude of publications from the 1950's and 1960's, and suggest that the product is innocuous.

c. *Benefit/risk ratio.* The benefit-to-risk assessment for this product appears to be satisfactory.

4. *Critique.* This fluid diphtheria toxoid has been shown to be safe, and the data from the literature support its efficacy when used as directed for primary immunization. No package insert is provided.

5. *Recommendations.* The Panel recommends that this product be placed in Category IIIC and that the appropriate license be revoked for administrative reasons because this product is not marketed in this country in the form for which licensed.

Diphtheria Toxoid Manufactured by Merrell-National Laboratories, Division of Richardson-Merrell, Inc.

Recommendations. The Panel recommends that this product be placed in Category IIIC and that the appropriate license be revoked for administrative reasons because this product is not marketed in the form for which licensed and consequently there are insufficient data on labeling, safety, and effectiveness.

Diphtheria Toxoid, Fluid, Manufactured by Parke, Davis & Company

1. *Description.* This is a fluid diphtheria toxoid containing 88 Lf of diphtheria toxoid per 0.5 mL dose. The

final product contains 0.5 percent glycerin, 1:10,000 thimerosal as a preservative, and is suspended in isotonic sodium chloride. A strain of *Corynebacterium diphtheriae* PW8 of proven toxigenicity is used for toxin production. Formaldehyde is used as the toxoiding agent, and the toxoid is then further purified by ultrafiltration, ammonium sulfate precipitation and subsequent dialysis.

This product is not currently on the market, but the manufacturer wishes to retain its license for possible future public health and medical demand.

2. *Labeling*—a. *Recommended use/indications.* No labeling was submitted.

b. *Contraindications.* No labeling was submitted.

3. *Analysis*—a. *Efficacy*—(1) *Animal.* This product meets Federal minimum requirements for diphtheria toxoid.

(2) *Human.* In 1961 to 1962, as part of a combined evaluation of diphtheria and tetanus toxoids, and poliomyelitis vaccine, a total of 61 prison inmates were given a variety of preparations containing Parke-Davis diphtheria toxoid singly or in combination with tetanus toxoid and poliomyelitis vaccine (Ref. 4). In most instances the doses administered probably elicited booster responses. It is not stated, however, where the products used were fluid or adsorbed toxoids. Furthermore, it was not clear whether the vaccines were experimental lots or the toxoids currently in use.

b. *Safety*—(1) *Animal.* This product meets Federal requirements for diphtheria toxoid.

(2) *Human.* No data were provided to substantiate the safety of this product.

c. *Benefit/risk ratio.* This cannot be determined in the absence of adequate data with regard to safety and efficacy.

4. *Critique.* This is a fluid diphtheria toxoid, currently licensed, but not marketed, which appears to meet animal efficacy and safety requirements. Satisfactory data have not been provided by which to assess either the safety or efficacy of this product in humans, whether used for primary or booster immunization.

No labeling has been submitted.

The Panel has a general concern about the present indications for the use of fluid diphtheria toxoid, in view of the greater and more durable immunity provided by adsorbed toxoids.

5. *Recommendations.* The Panel recommends that this product be placed in Category IIIC and that the appropriate license be revoked for administrative reasons because this product is not marketed in the form for which licensed and consequently there are insufficient data on labeling, safety, and effectiveness.

Diphtheria Toxoid Adsorbed Manufactured by Parke, Davis & Company

1. *Description.* This is an aluminum phosphate adsorbed diphtheria toxoid, containing 15 Lf per 0.5 mL dose, and 2.5 mg of aluminum phosphate per 0.5 mL dose. It is suspended in 0.9 percent saline, and 1:10,000 thimerosal is included as a preservative. The manufacturing process, clarified in a supplemental submission, defines the strain of *Corynebacterium diphtheriae* to be used, and outlines a process of ultrafiltration, ammonium sulfate precipitation, and subsequent dialysis. This product is not currently on the market, but the manufacturer wishes to retain its license for possible future public health and medical demand.

2. *Labeling*—a. *Recommended use/indications.* This product is said to be recommended for the active immunization of children from 6 months to 8 years of age, where a multiple antigen is not indicated. The labeling further states that this product may be used to immunize older children and adults, but with appropriate caution because of the possibility of reactions.

A complete immunizing treatment is said to consist of two 0.5 mL doses at intervals of 4 to 6 weeks. A recall dose 1 to 2 years after the initial course is recommended for full protection. The labeling was last revised in December 1964, and thus differs strikingly from current national recommendations.

b. *Contraindications.* No absolute contraindications are listed. Children with a negative Schick test are recommended not to receive diphtheria toxoid.

3. *Analysis*—a. *Efficacy*—(1) *Animal.* This product meets Federal requirements for diphtheria toxoid.

(2) *Human.* In 1961 to 1962, as part of a combined evaluation of diphtheria and tetanus toxoids, and poliomyelitis vaccine, prison inmates were immunized with various combinations of Parke-Davis diphtheria toxoids (Ref. 4). In most instances, the serologic responses obtained apparently represented booster reactions. Furthermore, it is not clear whether the products used were fluid or adsorbed diphtheria toxoid.

b. *Safety*—(1) *Animal.* This product meets Federal requirements for diphtheria toxoid.

(2) *Human.* There is adequate documentation of the safety in humans of Parke-Davis adsorbed diphtheria toxoids, as contained in the submission.

(c) *Benefit/risk ratio.* This cannot be determined with precision, owing to the absence of satisfactory data documenting the efficacy of this product when used as a primary immunizing agent. However, it is likely that the benefit-to-risk assessment would be satisfactory when the toxoid is used as a booster immunizing agent.

4. *Critique.* Since this product is not currently on the market, the labeling is badly out-of-date, and requires substantial revision in order to conform with current national recommendations for use of diphtheria toxoids. Furthermore, the statement that children with a negative Schick test do not require diphtheria toxoid is inappropriate, inasmuch as a Schick-negative child may become positive as time goes on, and therefore should have appropriate boosters as recommended in standard immunization schedules.

The Panel finds there is adequate documentation for the safety of this product, for that period of time when this product was previously on the market, as well as adequate documentation of its efficacy in humans when used as a booster immunization. Satisfactory data for the efficacy of adsorbed toxoid in humans, when used for primary immunization, have not been provided.

5. *Recommendations.* The Panel recommends that this product be placed in Category IIIC and that the appropriate license be revoked for administrative reasons because this product has not been marketed for a number of years in the form for which licensed and consequently there are insufficient data on labeling, safety, and effectiveness.

Diphtheria Toxoid, Fluid, Manufactured by Texas Department of Health Resources

1. *Description.* This is a fluid diphtheria toxoid which is purified and concentrated by the ammonium sulfate fractionation method. It is diluted in buffered saline and preserved in 1:10,000 thimerosal. It contains 120 Lf of diphtheria toxoid per mL.

2. *Labeling*—a. *Recommended use/indications.* The manufacturer recommends this product for use in infants and young children only when there is a contraindication to the administration of preparations of diphtheria toxoid combined with tetanus toxoid and pertussis vaccine. When necessary to administer the preparation to individuals less than 7 years of age, 3 injections of 1.0 mL subcutaneously are recommended at 3 to 4 week intervals. For the primary immunization of individuals greater than 7 years of age in is recommended that adult-type tetanus

and diphtheria toxoids be administered. There is no recommendation for reinforcing doses nor is a schedule for primary immunization of individuals 7 years of age or older provided.

b. *Contraindications.* It is a recommended that individuals 7 years of age and older should receive no more than 0.05 mL by injection without testing for sensitivity. Other contraindications are not specified.

3. *Analysis*—a. *Efficacy*—(1) *Animal.* This product meets Federal requirements.

(2) *Human.* Data directly related to this product are not available.

b. *Safety*—(1) *Animal.* This product meets Federal requirements.

(2) *Human.* No serious reaction has been reported related to the many thousand doses of the product distributed over the 10-year period.

c. *Benefit/risk ratio.* Although the risk from this preparation is low and the benefit is probably high, in the absence of human data no precise statement can be made regarding primary immunization. However, the benefit-to-risk assessment is satisfactory when the toxoid is used as a booster immunizing agent.

4. *Critique.* The Panel has a general concern about whether there are present indications for the use of fluid diphtheria toxoid, in the light of greater and more prolonged immunity provided by the adsorbed preparations. Furthermore, although this preparation is presumbly highly potent (120 Lf per dose), direct evidence of its superiority to, or comparability with adsorbed preparations as immunizing agents in humans is not available. Finally, the recommendations for its use are not consonant with those of advisory bodies in the United States.

5. *Recommendations.* The Panel recommends that this product be placed in Category I as regards its use for booster immunization and that the appropriate license(s) be continued provided that labeling is revised in accordance with the Panel's comments regarding labeling.

The Panel recommends that this product be placed in Category IIIA as regards its use for primary immunization and that the manufacturer's license for this product be maintained for a period not to exceed 3 years, during which time the manufacturer will be expected to provide satisfactory evidence of efficacy in humans under conditions of primary immunization. Labeling should be revised in accordance with the recommendations of this Report.

Diphtheria Toxoid Manufactured by Wyeth Laboratories, Inc.

The Panel recommends that this product be placed in Category IIIC and that the appropriate license be revoked for administrative reasons because this product is not marketed in the form for which licensed and consequently there are insufficient data on labeling, safety, and effectiveness.

Diphtheria Toxoid Adsorbed Manufactured by Wyeth Laboratories, Inc.

The Panel recommends that this product be placed in Category IIIC and that the appropriate license be revoked for administrative reasons because this product is not marketed in the form for which licensed and consequently there are insufficient data on labeling, safety, and effectiveness.

References

(1) BER Volume 2124.
(2) BER Volume 2111.
(3) BER Volume 2053.
(4) BER Volume 2003.

Generic Statement on Tetanus Toxoid

Tetanus is an acute disease of the nervous system caused by infection with the tetanus bacillus, *Clostridium tetani*, which produces an extremely potent neurotoxin that is lethal to man in miniscule amounts (approximately 7 millionths of a milligram). The tetanus bacillus also produces lesser reactive substances. The disease is of major importance, killing perhaps 1 million people worldwide annually, many of whom are newborns. The tetanus bacillus is probably primarily a resident of the intestinal tract of various animals, but spores are widely distributed in soil and dirt, and when carried into devitalized injured human tissue that is low in oxygen, the spore form of the bacillus can germinate, multiply, liberate toxin and hence cause the disease. The disease can be prevented by immunization with tetanus toxoid. Immunization is indicated for everyone, since natural immunity, if it exists at all, is exceedingly rare in man; not even the disease itself produces immunity in those who recover from it.

Because the morbidity and mortality of tetanus are largely a consequence of the toxin elaborated by the organism, antiserum (antitoxin) prepared by immunizing horses has been used for many decades in the treatment of the disease and for its prevention in exposed susceptible individuals. More recently the use of antitoxin prepared from horse serum has been largely replaced by the use of tetanus immune globulin (TIG) prepared from human serum. This approach to control of the disease is only partially successful because the disease may already be established by the time of treatment, and toxin that has been adsorbed and fixed to cells is unaffected by antitoxin or TIG. Penicillin or alternative effective antibiotic agents may eradicate the organism, but because they have no effect against toxin, antibiotics are only an adjunct to therapy. For these reasons, passive immunization with antitoxin or immune globulin and therapy with antimicrobial agents have been an unsatisfactory approach to treatment of the disease, and active immunization of humans against the toxin had been employed for many years.

Nature of Product

Tetanus toxoid is a formaldehyde detoxified bacteria-free filtrate of an anaerobic culture of a specially selected strain of *Clostridium tetani;* sometimes the culture is lysed before filtration to liberate more toxin. Toxin yields are comparable to those obtained with *Corynebacterium diphtheriae* and indeed the two toxins are, as protein molecules, remarkably similar despite the great differences in their pharmacologic action.

Production

Tetanus toxoid is produced with high yields in a simple liquid anaerobic medium, is detoxified with formaldehyde, is partially purified and thus freed of extraneous bacterial proteins, and in final dilution is administered in a dose similar to or slightly less (in terms of flocculation or Lf units) than that for diphtheria toxoid. The medium must contain no substance derived from horses, no know allergens, and no more than a specified trace of blood-grouping substances. Although tetanus toxoid has been widely and successfully used in the plain ("fluid") form, the superiority of aluminum salt-adsorbed tetanus toxoid has been clearly demonstrated, and this form of the toxoid is the most widely used.

Purification of tetanus toxoid is usually accomplished by methanol precipitation, by ammonium sulphate or metaphosphate purification, or less often by ultrafiltration. It is diluted to a concentration that will pass official requirements and a preservative (usually thimerosal) is added. It is subjected to the standard tests for sterility, safety, and potency required by the U.S. regulations.

The antigenicity in man of tetanus toxoid can vary considerably from preparation to preparation; this variation is partly due to variations in

the quality and content of toxoid (about 2 to 10 Lf) or of aluminum ion in the adjuvant. The protective level is assumed to be approximately 0.01 unit per mL of tetanus antitoxin toxoid. The geometric mean antibody titer response to various preparations in man after a single dose of either fluid or adsorbed toxoid is extremely variable, from less than 0.001 unit to 0.05 unit. However, with 2 doses of adsorbed toxoid, or 3 doses of fluid toxoid, this variation is greatly reduced and titers usually exceed the protective level.

Use and Contraindications

This product is often used singly as well as in combination with diphtheria toxoid (DT or Td) or with diphtheria toxoid and pertussis vaccine (DTP). The most commonly used product is DTP, which is routinely recommended for use in children 6 years and under in age; for older children and adults it is recommended that tetanus and diphtheria toxoids (combined) for adult use (Td) be employed for booster purposes. Tetanus toxoid is used singly by physicians who consider that the diphtheria component is either unnecessary, or likely to cause an untoward reaction in the patient. The fluid toxoid is given in 3 doses at least a month apart, with a fourth reinforcing dose, generally about 8 to 12 months later. The adsorbed form is given in 2 doses at least a month apart, with a reinforcing dose as in the case of fluid toxoid. Routine booster injections are recommended at 10 year intervals. In the case of wounds, boosters are recommended if the interval since the last booster is more than 5 years, and in the opinion of some, if the interval is more than 1 year.

In areas where neonatal tetanus is a problem, it can be virtually eliminated by administering either (1) two or more properly spaced doses of adsorbed toxoid to all women of child-bearing age, or (2) two or more doses of adsorbed toxoid during pregnancy, at least a month apart, with the second dose at least 2 and preferably 3 weeks before delivery.

Safety

Problems of adverse reactions to tetanus toxoid have been rare, especially since the elimination, over 30 years ago, of the highly allergenic Witte peptone from the production medium. Most of the local and febrile reactons that are seen appear to be related to more frequent inoculations than are necessary. In general, however, tetanus toxoid has an almost unique record for safety, no deaths having been associated with the administration of 2.5 million doses in a series reported from Denmark, where a thorough followup study was possible.

Manufacturers are required to record reported reactions.

Efficacy

When used as recommended, tetanus toxoid has provided protection to over 95 percent of those inoculated as judged by the induction of serum titers of at least 0.01 antitoxin unit per mL. Indeed, during World War II, only 4 properly immunized U.S. Army personnel developed tetanus among 2,500,000 persons wounded or injured. Other apparent failures have been reported, but in almost all instances they were associated with incomplete immunization or a false history of immunization.

Special Problems

Continued efforts should be made to establish, for routine lot-to-lot control, the usefulness of the quantitative technique of the evaluation of tetanus toxoids against the International Standards. This technique has been accepted by the European Pharmacopoeia. Direct human testing of any new or altered product should be required until such time as these efforts are completed. The Panel accepts the Bureau of Biologics' potency requirements in animals as evidence of adequate immunogenicity for use as a booster in man.

Historically, the antitoxin resonse to the initial 2 doses of adsorbed toxoid has been excellent. However, recent changes in manufacturing procedures may have resulted in lowering of the immunizing potency of tetanus toxoid in some products; hence, there is a need for reevaluating the primary antigenicity of current preparations in man.

Considerable confusion exists concerning the interchangeability of fluid and adsorbed toxoid. However, studies have shown the greater efficacy of adsorbed toxoid, not only in the magnitude but in the duration of the immune response. This superiority is particularly marked in combined active-passive immunization.

The incidence of reactions, though not of major importance, might be reduced by purification of the toxoid and by eliminating excessive booster doses in highly immunized persons.

Recommendations

There is a need for further studies on the World Health Organization-sponsored quantitative potency test in animals to establish the conditions under which the results are reproducible and to relate these results more closely to those obtained in immunization of man.

Efforts should be encouraged to enhance the immunogenicity of tetanus toxoid without increasing its reactogenicity so that fewer injections are required for primary immunization. Furthermore, it is essential to validate the immunogenicity in man of toxoids in current use that have not already been so tested. An illustrative protocol for such tests has been developed.

It is recommended that the immunogenic superiority of the adsorbed toxoid over the fluid preparation, especially with regard to the duration of protection, be emphasized and be included in labeling of products.

A minimum standard of purity should be established for tetanus toxoid.

Finally, for the tetanus toxoids whose effectiveness can be established by simple blood tests, there must be a resolution of the conflict in public policy between insistance on effectiveness data and constraints on obtaining such data resulting from the complex issue of informed consent. (See section 2.b. (2) in the Introduction in this Report.)

Basis for Classification

Past experience indicates that all tetanus toxoids that meet the Bureau of Biologics' requirements for potency in animal tests have proved effective as boosters in man. Therefore, all currently licensed and marketed products are classified in Category I as regards their use for secondary or booster immunization.

However, quantitative correlation between primary immunogenicity in man and the results of animal protection tests has not been established; therefore, direct testing of antitoxin responses in man is required, and should be repeated whenever significant changes in the manufacturing process are made. For those products; therefore, for which such evidence of effectiveness in primary immunization has not been acquired, Category IIIA is recommended.

References

(1) Edsall, G., "Current Status of Tetanus Immunization," *Archives of Environmental Health*, 8:731–741, 1964.

(2) Gottlieb, S., F.X. McLaughlin, L. Levine, W.C. Latham, and G. Edsall, "Long-term Immunity to Tetanus. A Statistical Evaluation and Its Clinical Implications," *American Journal of Public Health*, 54:961–971, 1964.

(3) Newell, K.W., D.R. LeBlanc, G. Edsall, L. Levine, H. Christensen, M.H. Montouri, and N. Ramirez, "The